A Systematic Review and Meta-Analysis of Hypoglycemia and Cardiovascular Events

A comparison of glyburide with other secretagogues and with insulin

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OBJECTIVE — Glyburide is the most widely used sulfonylurea but has unique pharmacodynamic properties that may increase harm. We hypothesized that glyburide causes more hypoglycemia and cardiovascular events than other secretagogues or insulin.

RESEARCH DESIGN AND METHODS — Data sources were Medline, Embase, Cochrane, and three other web-based clinical trial registers (1966–2005). Parallel, randomized, controlled trials in people with type 2 diabetes comparing glyburide monotherapy with monotherapy using secretagogues or insulin were selected. Outcomes were hypoglycemia, glycemic control, cardiovascular events, body weight, and death. Titles and abstracts of 1,806 publications were reviewed in duplicate and 21 relevant articles identified. Data on patient characteristics, interventions, outcomes, and validity were extracted in duplicate using predefined criteria.

RESULTS — Glyburide was associated with a 52% greater risk of experiencing at least one episode of hypoglycemia compared with other secretagogues (relative risk 1.52 [95% CI 1.21–1.92]) and with 83% greater risk compared with other sulfonylureas (1.83 [1.35–2.49]). Glyburide was not associated with an increased risk of cardiovascular events (0.84 [0.56–1.26]), death (0.87 [0.70–1.07]), or end-of-trial weight (weighted mean difference 1.69 kg [95% CI −0.41 to 3.80]) compared with other secretagogues. Limitations included suboptimal reporting of original trials. Loss to follow-up exceeded 20% in some studies, and major hypoglycemia was infrequently reported.

CONCLUSIONS — Glyburide caused more hypoglycemia than other secretagogues and other sulfonylureas. Glyburide was not associated with an increased risk of cardiovascular events, death, or weight gain.

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The global prevalence of diagnosed type 1 and 2 diabetes was estimated to be 2.8% in 2000 and projected to be 4.4% by 2030 (1). The UK Prospective Diabetes Study (UKPDS) showed that improving glycemic control reduced long-term microvascular complications (2). However, intensive therapy increases the risk for severe hypoglycemia, which is associated with mortality and morbidity (3,4).

Sulfonylurea drugs bind the sulfonylurea receptor, an ATP-sensitive K^+ channel, and inhibit potassium efflux, which facilitates insulin secretion (5). Compared with placebo, they reduce A1C levels by 1–2% (6). Differences in chemical structure, pharmacokinetic, and pharmacodynamic properties between sulfonylureas may lead to differences in the rates of hypoglycemic reactions. Glyburide (called glibenclamide in Europe), the most widely used sulfonylurea (7), has a relatively long terminal half-life in chronic dosing compared with other sulfonylureas, owing to its high affinity for the β-cell sulfonylurea receptor and the accumulation of active metabolites that are excreted through the kidney (7). Several observational studies have reported increased rates of hypoglycemia with the use of glyburide compared with other sulfonylureas (3,4). A systematic review of randomized controlled trials (RCTs) evaluating the risk for hypoglycemia associated with the use of glyburide has not, to our knowledge, been previously conducted.

The University Group Diabetes Program (UGDP) RCT (8) noted excess cardiac deaths in patients treated with tolbutamide; whether this was attributable to higher baseline cardiac risk in the patients allocated to tolbutamide or to a true biological effect has been widely debated. Consistent with the findings of the UGDP study, experimental laboratory data have suggested that sulfonylureas, particularly glyburide, might increase the risk of cardiovascular events. During coronary angioplasty, with each subsequent balloon dilatation, the extent of ST segment depression decreases and the time to onset of ST depression and the time to onset of angina increase. This phenomenon, known as ischemic preconditioning, is thought also to occur in acute coronary syndromes. Sulfonylurea-induced potassium efflux has been shown to reduce cardiac ischemic preconditioning in animal studies (9). In humans undergoing coronary angioplasty, the infusion of glimepiride has the same effect on ST depression and time to onset of angina as placebo, whereas the infusion of glyburide leads to a reduction in each of the effects of preconditioning (10).

This systematic overview of randomized controlled trials in people with type 2 diabetes was conducted to determine

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Abbreviations: FPG, fasting plasma glucose; RCT, randomized controlled trial; UKPDS, UK Prospective Diabetes Study; WMD, weighted mean difference.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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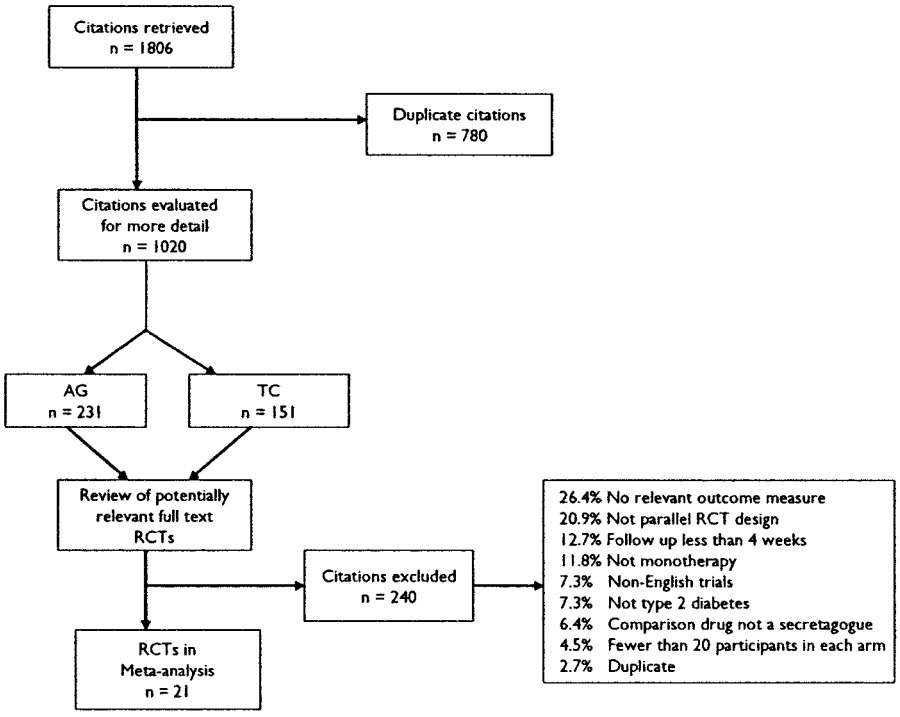

Figure 1—*Study flow diagram. AG, Azim S. Gangji; TC, Tali Cukierman.*

whether people taking glyburide are at increased risk for hypoglycemia or cardiovascular events compared with those taking other secretagogues (other sulfonylureas and meglitinides) or those taking insulin. For completeness of our analysis of important harms, we also examined weight gain.

RESEARCH DESIGN AND METHODS

We followed the recommendations of the Quality of Reporting of Meta-Analyses (QUOROM) conference (online appendix 1 [available at http://dx.doi.org/10.2337/dc06-1789]) (11).

Search strategy

We searched biomedical databases (Medline, Embase, the Cochrane library, clinicaltrials.gov, controlled-trials.com, and the U.K. national register of RCTs) and the bibliographies of relevant and review articles for reports of RCTs comparing glyburide with other secretagogues or with insulin. In Medline and Embase the searches combined generic and brand names of glyburide with key words specifying RCTs according to the strategy recommended by the Cochrane collaboration (online appendix 2) (12).

Two authors (A.S.G. and T.C.) independently reviewed this initial list (Fig. 1). Full text was obtained for all potentially appropriate articles and each was reviewed independently for eligibility.

Study selection

Eligible studies *1*) described people with type 2 diabetes; *2*) compared glyburide monotherapy with monotherapy using other sulfonylureas, meglitinides, or insulin; *3*) reported one or more of the following outcomes: hypoglycemia (major, minor, or all), cardiovascular events, or weight change; *4*) described a parallel design RCT; and *5*) were written in English. For hypoglycemia and cardiovascular events, we accepted the definition or outcome cluster reported in the original manuscript. Cardiovascular events included incident myocardial infarction, stroke, amputation, episodes of congestive heart failure, or cardiovascular death. Where multiple outcomes were reported, we selected the cluster that most closely matched the definition above. If no cluster was reported, we selected the single outcome we thought best represented cardiovascular outcomes. We excluded studies with <20 participants in each arm or a follow-up of <4 weeks. If studies were reported in more than one publication, we extracted data from the most recent article that met the inclusion criteria using data from related publications when necessary.

We used κ-statistics to express the extent of agreement between reviewers. Disagreements were resolved by consensus.

Validity assessment

We assessed validity in duplicate using the following criteria: *1*) method of randomization, *2*) presence of allocation concealment, *3*) blinding, *4*) loss to follow-up, and *5*) reporting of an intention-to-treat analysis.

Data abstraction

For each study, we abstracted, in duplicate: *1*) inclusion and exclusion criteria; *2*) baseline characteristics for the different treatment arms, including the number of participants at the start of the study; *3*) the intervention and comparator (including dose, frequency, target A1C, and A1C achieved); *4*) follow-up period and number of participants at study completion; and *5*) the definitions used to report hypoglycemia and cardiovascular events. For each treatment arm we abstracted: *1*) all episodes of hypoglycemia (number of participants with one or more episodes and number of episodes per unit of person-time), *2*) number of episodes of major and minor hypoglycemia, *3*) number of cardiovascular events, *4*) number of deaths from any cause, and *5*) weight change and end-of-trial weight. When the study included more than two arms, we chose the comparator with the largest number of people.

Data analysis

We summarized studies that compared glyburide with other secretagogues separately from studies that compared glyburide with insulin. Because of the unique pharmacokinetic and pharmacodynamic properties of glyburide, we prespecified a subgroup analysis comparing glyburide with other sulfonylureas.

We assessed patient characteristics, interventions, and outcomes for clinical heterogeneity and used the I^2 statistic to quantify the proportion of total variation that was due to statistical heterogeneity. We calculated relative risk (RR) and 95% CIs to summarize the effect size for dichotomous outcomes (number of participants with at least one hypoglycemic event, number of major and all hypoglycemic events, cardiovascular events, and overall mortality), and rate ratios and 95% CIs were calculated for event rates. For continuous data, we calculated the weighted mean difference (WMD) for each study and summarized this as an

overall WMD and 95% CI. We used random effects assumptions throughout.

To assess for publication bias, we constructed a funnel plot of the SE of the log of the RR plotted against the RR for experiencing at least one episode of hypoglycemia.

We used MetaView 4.2 in Cochrane Review Manager 4.2 (Cochrane Collaboration, Oxford, U.K.) and Comprehensive Meta-Analysis 2.2 (Biostat, Englewood, NJ). $P < 0.05$ was considered statistically significant, and an I^2 value of >50% indicated excess statistical heterogeneity.

RESULTS

Search

We identified 1,806 publications, of which 21 articles describing 20 studies were relevant (Fig. 1) (2,13–32). Estimated κ for agreement on relevance was 0.86 (95% CI 0.81–0.91). Of the 21 articles, 12 compared glyburide with an oral hypoglycemic agent and reported this as patients experiencing at least one episode of hypoglycemia (13,15–17,20,21,23, 25–27,29,30); an additional 3 articles only reported total number of hypoglycemic episodes (14,18,19); 3 articles compared glyburide with insulin (22, 27,31); and 3 studies only reported a change in weight (24,28,32).

Validity assessment

Five of the 21 studies described the method of randomization (2,14,22, 30,33); 3 of these used a computer generated method (2,22,27). The method of allocation concealment was described only in the UKPDS trial, which used consecutive opaque envelopes. Seven studies reported blinding of participants and caregivers (13,15,16,19–21,25). The UKPDS study reported that there was blinding of outcome assessors and data analyzers (2).

Twelve of the 21 studies reported the use of an intent-to-treat analysis (13,15–17,20,21,23,25–27,29,30). Loss to follow-up was reported in 19 studies (2,14–23,25–32). There was a large amount of variability (0–37%) in the percentage of patients lost to follow-up. Reasons for loss to follow-up included inadequate glycemic control, hypoglycemia, other adverse events, noncompliance, and moving out of the study area.

Study characteristics

Included studies reported on 7,047 people with follow-up periods from 1 month to 10 years. Some of the studies specified the target A1C or fasting plasma glucose (FPG) to be achieved. Though this value varied widely between studies, the target level was always identical for the two arms within each study (2,14–16,18,20–23,25,27,28). Hypoglycemia was defined as symptoms (without a threshold glucose level) in some studies and in others as symptoms coexisting with low capillary blood glucose levels (minimum threshold 48 mg/dl [2.7 mmol/l], maximum 63 mg/dl [3.5 mmol/l]). Major hypoglycemia was defined as an episode requiring assistance or hospital admission. Details of study characteristics and study validity are available in the online appendix (Tables A and B).

Quantitative data synthesis

Table 1 provides a summary of effect sizes, 95% CIs, and I^2 values for the meta-analyses of harms.

Hypoglycemia and glycemic control

Figure 2 shows a 52% greater risk of experiencing at least one episode of hypoglycemia for participants receiving glyburide compared with those receiving other secretagogues (RR 1.52 [95% CI 1.21–1.92]). In the planned subgroup analysis comparing glyburide with other sulfonylureas, glyburide was associated with an 83% higher risk of causing at least one episode of hypoglycemia (1.83 [1.35–2.49]).

Five studies compared glyburide with other secretagogues and reported their results as total number of hypoglycemic episodes (14,15,19,20,26) (Table 1). These studies were heterogeneous (I^2 76.8%). There was an 80% higher rate of hypoglycemic episodes with glyburide (rate ratio 1.80 [95% CI 1.06–3.09]) compared with other secretagogues. Limiting the analysis to studies comparing glyburide with other sulfonylureas led to a decrease in heterogeneity to within acceptable limits (I^2 17.6%); the increased risk associated with glyburide compared with other sulfonylureas was 44% (1.44 [1.13–1.85]) (14,15). Two studies, both using a sulfonylurea as a comparator (14,15), reported major hypoglycemic episodes. The risk of major hypoglycemic events was over four times higher for glyburide compared with other sulfonylureas (4.69 [0.78–28.08]); however, this was not statistically significant.

Studies reporting A1C were all comparisons of glyburide with sulfonylureas: no significant difference was identified

Table 1—*Summary of risk of hypoglycemia, cardiovascular events, death, and weight change: glyburide compared with all secretagogues, sulphonylureas, or insulin*

Comparator	Patients with any hypoglycemic episode [RR (95% CI) I^2]	Patients with a major hypoglycemic episode [RR (95% CI) I^2]	All hypoglycemic episodes per patient-year [rate ratio (95% CI) I^2]	Major hypoglycemic episodes per patient-year [rate ratio (95% CI) I^2]	Cardiovascular events [RR (95% CI) I^2]	Death [RR (95% CI) I^2]	Weight gain (kg) [WMD (95% CI) I^2]
All secretagogues	1.52 (1.21–1.92) 42.1%	ND	1.80 (1.06–3.09) 76.8%*	ND	0.84 (0.56–1.26) 12.6%	0.87 (0.70–1.07) 0%	1.69 (−0.41 to 3.80) 31.4%
Sulphonylureas	1.83 (1.35–2.49) 43.4%	ND	1.44 (1.13–1.85) 17.6%	4.69 (0.78–28.08) 0%	0.92 (0.71–1.19) 0%	0.79 (0.47–1.32) 33.7%	2.49 (−0.48 to 5.47) 4.9%
Insulin	0.88 (0.25–3.06) 92.5%*	ND	0.089 (0.019–0.408) 83.1%*	ND	0.89 (0.70–1.14) NA†	0.97 (0.79–1.20) NA‡	−2.28 (−2.42 to −2.14) 0%

*Estimate unreliable due to heterogeneity. †No data on cardiovascular outcome clusters but data on myocardial infarction extracted from single study (UKPDS 33). ‡Data from single study (UKPDS 33). NA, not applicable; ND, no data.

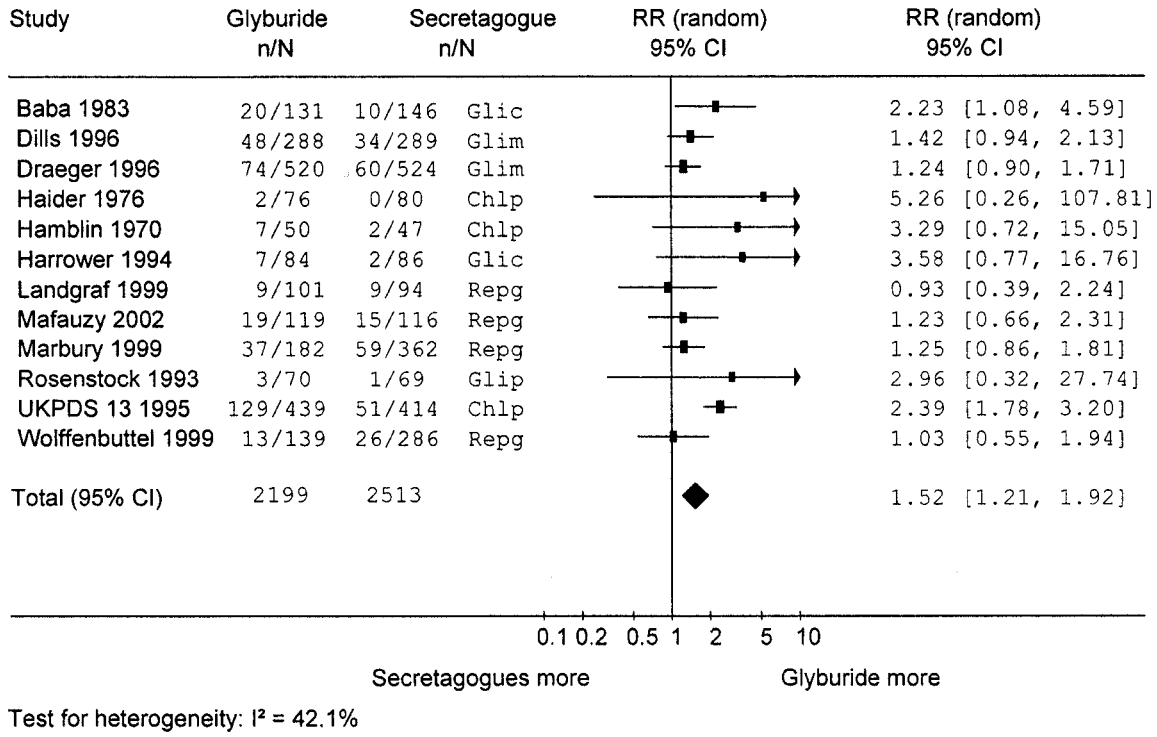

Figure 2—*RR for experiencing at least one hypoglycemic episode: glyburide versus other secretagogues. Chlp, chlorpropamide; Glic, glicazide; Glim, glimiperide; Glip, glipizide; Repg, repaglinide.*

(A1C WMD −0.13% [95% CI −0.52 to 0.26; I^2 43.7%]). Reports of FPG comparing glyburide with other secretagogues were heterogeneous (WMD −0.49 mmol/l [95% CI −1.15 to 0.18; I^2 97.9%]). Heterogeneity was not present in the analysis comparing FPG for glyburide with other sulfonylureas. There was a small effect in the direction of improved FPG with glyburide (WMD −0.34 mmol/l [95% CI −0.40 to −0.27; I^2 0%]).

Three studies (1,339 participants) showed that the risk of hypoglycemia was similar for people treated with glyburide and those treated with insulin, though CIs were wide (RR 0.88 [95% CI 0.25–3.06]) (22,27,31).

Weight change and end-of-trial weight

End-of-trial weight was reported in three studies of 498 people comparing glyburide with other secretagogues (25,27,30). Overall, glyburide did not cause an increase in weight compared with other secretagogues (WMD 1.69 kg [95% CI −0.41 to 3.80]). However, in the three studies of 1,840 people comparing glyburide with insulin, body weight increased by 2.28 kg more in people treated with insulin than in those treated with glyburide (WMD −2.28 kg [−2.42 to −2.14]) (2,18,22).

Cardiovascular events and overall mortality

Cardiovascular events were reported in three studies including 2,822 participants (2,15,21). There was no significant difference between glyburide and secretagogues (RR 0.84 [95% CI 0.56–1.26]). The same three studies reported no significant difference in overall mortality (0.87 [0.70–1.07]). There were no studies that reported a cardiovascular outcome cluster for glyburide compared with insulin. However, the UKPDS 33 (2) study reported data from which the RR of myocardial infarction for glyburide compared with insulin could be calculated: RR 0.89 (95% CI 0.70–1.14). One study (UKPDS 33) reported data from which mortality for glyburide compared with insulin could be calculated: 0.97 (0.79–1.20).

Assessment of publication bias

Visual inspection of the funnel plot of the outcome "number of participants experiencing at least one hypoglycemic episode" demonstrated a paucity of studies with large SEs to the left of the overall estimate (available from the authors upon request).

CONCLUSIONS

— The main findings of this meta-analysis are that glyburide caused more hypoglycemia than other secretagogues and more hypoglycemia than other sulfonylureas. In the meta-analysis of the two studies that reported major hypoglycemia, there was a trend toward a greater number of events in patients treated with glyburide than with other sulfonylureas. The direction of effect was consistent in all analyses (Table 1). UKPDS 33 reported the percentage of patients per year with one or more episodes and with one or more major episodes of hypoglycemia. Although we were unable to include these results in our meta-analysis because of the method of reporting, our results (glyburide vs. other sulfonylureas RR 1.83 [95% CI 1.35–2.49]) are consistent with the findings of UKPDS 33, in which the mean percentage of patients per year with one of more episodes of hypoglycemia was 17.7% for glyburide and 11.0% for chlorpropamide (RR 1.61), and the mean percentage of patients per year with one or more major hypoglycemic episodes was 0.6% for glyburide and 0.4% for chlorpropamide (RR 1.50).

We did not find a difference in A1C between patients treated with glyburide and those treated with other sulfonyl-

ureas; however, there was a small, statistically significant difference of questionable clinical importance in the comparison of FPG between these two groups. On the evidence of the A1C results, it seems unlikely that improved glycemic control accounts for the increase in hypoglycemia observed.

We did not find any difference in risk for hypoglycemia of glyburide compared with insulin. CIs for this estimate are wide, so a difference cannot be excluded. Other reasons for finding no difference include: *1*) inadequate titration of insulin toward achieving glucose control (in one of the studies included in this review, the achieved end-of-trial A1C in the insulin arm was 8.5% [22]), *2*) the small dose adjustments possible with insulin that are not possible with an oral agent, or *3*) that the difference is minimized in patients with newly diagnosed disease who predominated in our analysis.

Though data from animal and human studies suggest that glyburide might exacerbate coronary ischemia more than other secretagogues and specifically more than other sulfonylureas (10), the meta-analysis of cardiovascular events and deaths provided no support for the hypothesis that these effects lead to adverse cardiovascular outcomes. In addition, weight gain with glyburide was similar to that observed with other sulfonylureas and less than that observed with insulin.

Methodological limitations

Limitations of the included studies. The method of randomization and allocation were seldom described in the studies reported here. Lack of allocation concealment may significantly influence observed treatment effects (34).

There was great variability between studies in the loss to follow-up, from 0 to 37%. Since hypoglycemia and loss to follow-up have been shown to be associated (19,26), differential follow-up of patients prone to hypoglycemia would lead to underestimation of the absolute rates of hypoglycemia in all studies and might also change the differential effect between groups in those studies with a large percentage of patients lost to follow-up.

Follow-up time was short in the majority of studies, limiting the power to detect differences in cardiovascular event rates.

Limitations of overall review. We did not include studies published in languages other than English in our review. The lack of inclusion of non-English articles has been identified as a source of bias in some circumstances (35). However, a recent retrospective analysis suggests that excluding trials published in languages other than English has generally little effect on summary treatment effect estimates (36).

There was a paucity of studies with larger SEs to the left of the point estimate in the funnel plot. Larger SEs can be due to either smaller sample size trials, studies with more variability, or both. This may suggest publication bias or a systematic error introduced by the loss to follow-up.

Statistically significant and clinically important results were obtained for the meta-analyses of all episodes of hypoglycemia, most of which would likely have been minor. Though the clinical importance of minor hypoglycemia can be questioned, minor hypoglycemia has been shown to predict major hypoglycemia (37), and minor episodes lead to disruptions in glycemic control (38,39) that are thought to have long-term consequences (40). Although power to detect a difference in the analysis of major hypoglycemia was limited by the low number of studies reporting this outcome, seven of the eight major hypoglycemic episodes reported occurred in glyburide-treated patients (14,15). UKDPS 33 results, which were not reported in a format that enabled us to include them in the meta-analysis, also show consistency between major episodes and all episodes in the direction and magnitude of the RR when glyburide is compared with chlorpropamide (see above), lending weight to the hypothesis that minor episodes may be a useful surrogate for more clinically important major episodes.

Because all of our comparisons are with glyburide, we are unable to draw any conclusions about the properties of other drugs compared with one another.

Finally, statistical heterogeneity was noted between the studies comparing the risk of at least one hypoglycemic episode in people taking glyburide compared with those taking other secretagogues. Despite this statistical heterogeneity, visual inspection shows that glyburide consistently caused more hypoglycemia than other secretagogues. This statistical heterogeneity most likely results from the relatively tight CI around the UKPDS 13. Indeed, when the UKPDS data were removed from the analysis, the studies were deemed homogenous without a significant change in the overall estimate (*P* value increased from 0.06 to 0.64 and I^2 decreased from 42.1 to 0% with the overall RR estimate changing from 1.52 to 1.33, both statistically significant).

Implications for practice

In 2003, it was estimated that 13.8 million people in the U.S. had established type 2 diabetes; of these, 7.8 million people used at least one oral antidiabetes medication (41). Glyburide, available as a generic, is relatively inexpensive and widely used. Our results suggest that risk of hypoglycemia and rates of hypoglycemia for millions of patients are likely ~50% higher in those taking glyburide than they would be if they were taking an alternative sulfonylurea or nonsulfonylurea secretagogue.

Implications for research

Our review highlights the importance of minimizing loss to follow-up in RCTs of long duration, as our overall estimates included some clinical trials in which loss to follow-up exceeded 20%. The clinical consequences of hypoglycemia, its effects on patient compliance, and the direct health care costs of hypoglycemia are all important issues that warrant inclusion in an economic evaluation of the relative cost-effectiveness of glyburide compared with other secretagogues.

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